Irinotecan Pathway Genotype Analysis to Predict Pharmacokinetics

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ABSTRACT

Purpose: The purpose was to explore the relationships between irinotecan disposition and allelic variants of genes coding for adenosine triphosphate binding cassette transporters and enzymes of putative relevance for irinotecan.

Experimental Design: Irinotecan was administered to 65 cancer patients as a 90-min infusion (dose, 200–350 mg/m²), and pharmacokinetic data were obtained during the first cycle. All patients were genotyped for variants in genes encoding MDRI P-glycoprotein (ABCB1), multidrug resistance-associated proteins MRP-1 (ABCC1) and MRP-2 (canalicular multispecific organic anion transporter; ABCC2), breast cancer resistance protein (ABCG2), carboxylesterases (CES1, CES2), cytochrome P450 isozymes (CYP3A4, CYP3A5), UDP glucuronosyltransferase (UGT1A1), and a DNA-repair enzyme (XRCC1), which was included as a nonmechanistic control.

Results: Eighteen genetic variants were found in nine genes of putative importance for irinotecan disposition. The homozygous T allele of the ABCB1 1236C>T polymorphism was associated with significantly increased exposure to irinotecan (P = 0.038) and its active metabolite SN-38 (P = 0.031). Pharmacokinetic parameters were not related to any of the other multiple variant genotypes, possibly because of the low allele frequency. The extent of SN-38 glucuronidation was slightly impaired in homozygous variants of UGT1A1*28, although differences were not statistically significant (P = 0.22).

Conclusions: It is concluded that genotyping for ABCB1 1236C>T may be one of the factors assisting with dose optimization of irinotecan chemotherapy in cancer patients. Additional investigation is required to confirm these findings in a larger population and to assess relationships between irinotecan disposition and the rare variant genotypes, especially in other ethnic groups.

INTRODUCTION

The topoisomerase I inhibitor irinotecan has a major role in the management of metastatic colorectal cancer and has been approved either in combination with 5-fluorouracil and folinic acid in the first line treatment setting or as monotherapy in the second line setting (1). In clinical use, irinotecan is subject to very substantial interindividual variability in pharmacokinetic behavior, treatment efficacy, and the occurrence of unpredictable, sometimes severe toxic side effects that might be life threatening in some patients (2). Potential causes for such variability in drug effects include the pathogenesis and severity of the disease being treated, the occurrence of unintended drug interactions, and impairment of hepatic and renal function or both (3, 4). Despite the potential importance of these clinical variables in determining drug effects, it is now recognized that inherited differences in the metabolism and excretion into the feces and urine can have an even greater impact on the efficacy and toxicity of drugs (5).

The metabolism of irinotecan is very complex, and involves several Phase I and II metabolizing enzymes (Fig. 1). In humans, the ester bond of irinotecan is cleaved by CESs to form the primary pharmacologically active metabolite SN-38 (6), which is further conjugated by UGT isoenzymes to form an inactive β-glucuronic acid conjugate, SN-38G (7). Another prominent pathway of irinotecan metabolism consists of a CYP3A4-mediated oxidation of the bipiperidine side chain attached to the core structure, which results in the formation of a major metabolite identified as APC (8). The pharmacological behavior of irinotecan is additionally complicated by the fact that its elimination pathways are partially mediated by membrane-localized, energy-dependent outward drug pumps that facilitate cellular efflux mechanisms (Fig. 1). These proteins belong to the superfamily of ABC transporters and include MDRI P-glycoprotein (ABCB1; Ref. 9), multidrug resistance-
associated protein 1 (ABCC1; Ref. 10), and its homologue multidrug resistance-associated protein 2 [also referred to as canalicular multispecific organic anion transporter or ABCC2; Ref. (11)], and breast cancer resistance protein [also referred to MXR or ABCG2; Ref. (12)]. The aim of this study was to link genetic polymorphisms in transporters and enzymes involved in irinotecan elimination to interindividual differences in measures of drug exposure and to provide a stronger scientific basis for optimizing irinotecan therapy on the basis of each patient’s genetic constitution.

PATIENTS AND METHODS

Patients and Treatment. Patients with a histologically confirmed diagnosis of a malignant solid tumor for which there was no effective standard regimen and irinotecan was a reasonable treatment option were treated with a 90-min i.v. infusion of irinotecan. The drug was given once every 3 weeks until progression of disease or dose-limiting toxicities appeared and was given as a single agent at a dose of 350 mg/m² or as part of a combination chemotherapy regimen with cisplatin at doses ranging between 200 and 300 mg/m². All patients were treated between January 1997 and June 2001 at the Erasmus MC-Daniel den Hoed Cancer Center (Rotterdam, the Netherlands). Inclusion criteria included the following: (a) adequate hematopoietic function (neutrophil count, \(> 2.0 \times 10^9\) liter and platelet count, \(> 100 \times 10^9\) liter); and (b) normal renal and hepatic functions (serum creatinine concentration, \(< 135 \mu\text{mol/liter and/or creatinine CL, } > 60 \text{ ml/min; serum AST and ALT concentrations, less than three times the upper limit of normal, and less than five times the upper limit of normal in case of liver metastasis). None of the patients received other drugs, dietary supplements or herbal preparations known to interfere with irinotecan pharmacokinetics. The clinical protocols, including blood sampling for the purpose of pharmacokinetic and pharmacogenetic analyses, were approved by the Erasmus MC Ethics Board, and all patients provided written informed consent before study entry.

Pharmacokinetic Data Analysis. In view of the small intrasubject variability in irinotecan pharmacokinetic parameters (2), blood samples of \(- 5 \text{ ml}\) were only collected during the first cycle of treatment. The sampling was performed at the following time points: immediately before infusion; at 30 min after the start of the infusion; 5 min before the end of infusion; and at 10, 20, and 30 min and 1, 1.5, 2, 4, 5, 8.5, 24, 32, and 48 h after the end of infusion. In 37 of 65 patients, additional blood samples were taken at 56, 196 (day 8), 360 (day 15), and 500 h (day 21) after the end of infusion. Blood samples were handled as outlined (13), and concentrations of irinotecan, SN-38 APC, and SN-38G were determined in all patients by reversed-phase high-performance liquid chromatography with fluorescence detection as described in detail elsewhere (14). Concentrations of SN-38G and APC in plasma were measured in only 53 and 12 patients, respectively, because of limited sample supply that precluded an additional analysis on the same material.

Previously developed population pharmacokinetic models were used to predict the pharmacokinetic parameters of the lactone and carboxylate forms of the analytes (15). The considered parameters included CL, volume of distribution in the central compartment, and the dose-normalized accumulated AUC. The latter parameter was simulated for irinotecan and its metabolites in all patients from time 0 to 100 h after start of infusion (AUC\(_{0-100\text{ h}}\)) for a 90-min i.v. infusion and a standard dose of 350 mg/m². This data analysis was performed using NONMEM version VI (S. L. Beal and L. B. Sheiner, San Francisco, CA). Metabolic ratios were calculated as the AUC ratio of SN-38 to irinotecan (relative extent of conversion), the AUC ratio of SN-38G to SN-38 (REG), and the AUC ratio of APC to irinotecan (relative extent of metabolism). To allow for a comparative analysis with literature data (16), the REG in each

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**Fig. 1** Pathway of genes with a putative role in regulating irinotecan disposition.
<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Forward primer 5'-'3'</th>
<th>Reverse primer 5'-3'</th>
<th>Annealing temp (°C)</th>
<th>Product size (bp)</th>
<th>Pyrosequencing primer 5'-3'</th>
<th>RFLP Restriction enzyme</th>
</tr>
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<tr>
<td>ABCB1 1236 C&gt;T</td>
<td>GGTGTCTGTGAATGCCTTGAG</td>
<td>CTCCTGATCAGCTGACGTGT</td>
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<td>148</td>
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<td>AAGCAGATGGAATGACCTGA</td>
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<td>136</td>
<td>GGTGGAGCCAGCAATTCATAC</td>
<td>MboII</td>
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<td>GAGGCCCTCCTTGCTTGCTGTG</td>
<td>GCTATGTGGCTCCTCTTT</td>
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<td>250</td>
<td>GTGTCAGTCACAGGAGA</td>
<td>HhaI</td>
</tr>
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<td>ABC1 14008 G&gt;A</td>
<td>AGGGCCTTTTGACGCAAGGTG</td>
<td>TCTTGACGCGGAGTTG</td>
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<td>214</td>
<td>AATAAGCCAGGCTCA</td>
<td>MseI</td>
</tr>
<tr>
<td>ABC1 462 G&gt;T</td>
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<td>CCCCACCTTTGTCCTACTC</td>
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<td>197</td>
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<td>AAAGCAACATTTTGCTGCT</td>
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<tr>
<td>CES2 1647 C&gt;T</td>
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<td>AGGGACAGCCCATAGGACGAGA</td>
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<td>ATCTCCTAATCTTACAAATTCACGTA</td>
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<td>ATTAGGGTGCAAGACAGA</td>
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<td>176</td>
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<td>ATTTCCCACCCATCTTCTAA</td>
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<td>291</td>
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<tr>
<td>XRC1 26304 C&gt;T</td>
<td>TTCTCCCTGCTCTCCACC</td>
<td>CTACCCATCCCTCAGAGACC</td>
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<td>PovII</td>
<td></td>
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<tr>
<td>XRC1 27466 G&gt;A</td>
<td>CCTGAGATTTCTGCTCTTG</td>
<td>AGCCACTGACCCACTACCTAC</td>
<td>60</td>
<td>640</td>
<td>PovII</td>
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<tr>
<td>XRC1 28152 G&gt;A</td>
<td>GCCCCTCAGATGACACCTTAA</td>
<td>TCCCGCCCTCTTCTAAGT</td>
<td>60</td>
<td>593</td>
<td>NciI</td>
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</table>

a Biotinylated.
b N/a, not applicable.
individual patient was also calculated on the basis of the linear trapezoidal-rule AUC values from time 0 to 24 h after start of infusion, without extrapolation to infinity, with uniform weighting using noncompartmental analysis in WinNonLin version 3.0 (Pharsight Corp., Mountain View, CA).

Pharmacogenetic Data Analysis. Genomic DNA was extracted from 1 ml of whole blood or plasma using the Gentra PureGene Blood kit (Gentra, Minneapolis, MN) and the QIAamp DNA Blood midi kit (Qiagen, Inc., Valencia, CA), respectively, following the manufacturers instructions, and was reconstituted in a buffer containing 10 mM Tris (pH 7.6) and 1 mM EDTA. SNPs and other genetic variations were identified from the literature or were mined using the publicly available SNP databases (17).

Variations in the ABCB1 (nucleotide 1236C>T, 2677G>T/A, and 3435C>T), ABCCI (14008G>A, 462C>T, and 34215C>G), ABCG2 (156231A>G), CES1 (1440A>T, 1525A>C), CES2 (1647C>T), CYP3A4 (CYP3A4*1B, CYP3A4*2, and CYP3A4*3), CYP3A5 (CYP3A5*3C and CYP3A5*6), UGT1A1 (UGT1A1*7 and UGT1A1*28), and XRCCI (26304C>T, 27466G>A, and 28152G>A) genes were analyzed by PCR-RFLP or by Pyrosequencing (Table 1). Variations in the XRCCI gene were included as negative controls. PCR for ABCB1 3435C>T and UGT1A1*28 was carried out as described previously (18, 19).

All other PCR primers were designed using Primer Express version 1.5 (ABI, Foster City, CA), and the Pyrosequencing primers were designed using the Pyrosequencing SNP Primer Design Version 1.01 software.5 RFLP sites were determined using Rebase.6 The PCR primers, conditions, and restriction enzymes (NEB, Beverly, MA) used in the current study are listed in Table 1. PCR was carried out using AmpliTaq Gold PCR master mix (ABI), 5 pmol of each primer, and 10–50 ng of DNA isolated from whole blood or DNA from 1 μl of undiluted plasma. Pyrosequencing was carried out as previously described (20) using the Pyrosequencing AB PSQ96 instrument and software (Uppsala, Sweden). RFLP results were analyzed by electrophoresis using 4% agarose (Promega Corporation, Madison, WI). The genotype was called variant if it differed from the Refseq consensus sequence for the SNP position.7 Genotype frequency analysis of Hardy-Weinberg equilibrium was carried out using Clump version 1.9 (21). Linkage disequilibrium between different pairs of SNPs was determined in terms of the classical statistic D’. The absolute value for D’ (|D’|) of 1 denotes complete linkage disequilibrium, whereas a value of 0 denotes complete linkage equilibrium (22).

Statistical Considerations. All pharmacokinetic data are presented as mean values ± SD, unless stated otherwise. To relate pharmacokinetic parameters with each polymorphism, a nonparametric Kruskal-Wallis test was used after a logarithmic transformation for data with a skewed distribution. These statistical calculations were performed using SPSS version 9.0 (Paris, France) with an a priori cutoff of P < 0.05. To relate REG with the UGT1A1*28 polymorphism, a nonparametric-trend analysis was conducted using Stata version 7.0 (Stata Corp., College Station, TX), as described previously (16).

RESULTS

Patients and Pharmacokinetics. A total of 65 adult cancer patients (32 males and 33 females) with a median age of 53 years was enrolled onto this study (Table 2). The majority of patients was European Caucasian, the most prominent disease type was a gastrointestinal malignancy, and 62 of 65 individuals received single agent irinotecan (51 at a dose level of 350 mg/m2). The observed plasma concentration-time profiles of irinotecan and its metabolites SN-38, SN-38G, and APC were well predicted by previously defined NONMEM models (15), as indicated by goodness-of-fit plots (data not shown). The individual and mean pharmacokinetic parameters of irinotecan and its metabolites are consistent with previous findings from patients on a similar regimen (2), showing extensive glucuronidation of SN-38 with wide interindividual variability (Table 3). All AUC ratios found in this group of patients were highly variable, with up to 6-, 22-, and 15-fold difference between the lowest and highest values for relative extent of conversion, REG, and relative extent of metabolism, respectively (Table 3).

Genotyping. Seventeen SNPs and 1 dinucleotide repeat were analyzed in nine genes of putative relevance for irinotecan disposition (Fig. 1), and 3 SNPs in one gene likely to act downstream of topoisomerase I inhibition (i.e., XRCCI; Ref. 23). XRCCI was included as a control gene of unlikely signif-
Comparison of pharmacokinetic data in patients wild-type versus heterozygous for CYP3A4*3 suggested that the CL of irinotecan lactone might be reduced and that the AUC might be increased in the heterozygotes, although these differences were not statistically significant, presumably as a result of the small sample size \( (P = 0.059 \text{ and } P = 0.070, \text{ respectively}) \). Statistically significant differences were also not observed in pharmacokinetic parameters, including REG (Table 6), among variants in UGT1A1*28 (wild type > heterozygous variant > homozygous variant, \( P > 0.22 \)).


discussion

The desire for better tools to individualize chemotherapy has led to new ways of evaluating patients. The observation that most chemotherapy agents have a high degree of variability in drug disposition has prompted the use of genetics to try and identify the mechanistic basis for this variation. Previous investigations have shown that pharmacogenetic testing may contribute to the individualization of drug treatment and hence may have an increasing impact on enhanced drug safety and efficacy (5).

In this study, exploratory relationships were assessed between disposition characteristics of irinotecan and 21 allelic variants of 10 genes coding for various ABC transporters and drug-metabolizing enzymes in a group of 65 cancer patients.

The most relevant finding of this study was an apparent association between the presence of the homozygous T allele of ABCB1 1236C>T (located at exon 12) and increased exposure to both irinotecan and SN-38. This appears to be the first in vivo observation that this allelic variant may be functionally polymorphic in that it alters the activity of the encoded protein in relation to the wild-type and heterozygous sequences. ABCB1 1236C>T is a synonymous cSNP located in codon 411 of the P-glycoprotein. It is unlikely that this variation directly affects the expression of P-glycoprotein. However, it may have an indirect effect such as altering RNA stability. A comprehensive analysis of all DNA variations in this gene is warranted to uncover the basis of the association between P-glycoprotein and irinotecan and SN-38 exposure.

Previously, Hoffmeyer et al. (26) found an association between ABCB1 3435C>T at exon 26 and increased exposure to the P-glycoprotein substrate drug digoxin after oral administration. Although this SNP is also a silent polymorphism, intestinal P-glycoprotein expression was significantly decreased, leading to increased absorption of the drug. More recently, a study was published that confirmed the functional importance of ABCB1 3435C>T polymorphism, although in this case, the variant allele was associated with lower plasma concentrations of the oral antiretroviral drugs nevirapin and efavirenz (27).

To explain this paradox, it was hypothesized that low levels of P-glycoprotein expression might be compensated for by overexpression of other ABC transporter proteins with affinity for these antiretroviral drugs and/or the induction of CYP3A isoforms (27). In our study, neither the ABCB1 3435C>T nor the ABCB1 2677G>T/A SNP was associated with altered plasma concentrations of irinotecan and/or its metabolites. The latter mutation leads to the replacement of Ala to Ser or Thr but does not appear to result directly in an altered expression of P-glycoprotein (28).
Recent investigations indicated that the metabolism of irinotecan is substantially influenced by a nucleotide polymorphism in the TATA-box sequences of UGT1A1. This gene encodes the enzyme UGT1A1 that is responsible for the glucuronidation of several compounds, including SN-38 (7). An extra (7th) TA-repeat [A(TA)$_n$]TAA in one allele results in ~70% reduction in transcriptional activity compared with wild-type UGT1A1 [A(TA)$_n$TAA]. Inheritance of the promoter containing [A(TA)$_n$]-TAA] is one of the most common genotypes leading to Gilbert’s syndrome (29), which is characterized by mild nonhepatic, unconjugated bilirubinemia. Genetic abnormalities in UGT1A1 are also associated with the Crigler-Najjar hepatic syndromes with absent (type I) or reduced (type II) UGT1A1 activity (29). As such patients cannot adequately metabolize SN-38, they might be at increased risk for severe drug-related toxicities. Indeed, it has been suggested that screening for

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Genotype and Allele frequencies for the studied genes</th>
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</thead>
<tbody>
<tr>
<td>Polymorphism*</td>
<td>Nomenclature</td>
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<tr>
<td>ABCB1 1236 C&gt;T</td>
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</tr>
<tr>
<td>ABCB1 3435 C&gt;T</td>
<td>n/a</td>
</tr>
<tr>
<td>ABCB1 2677 G&gt;T/A</td>
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<tr>
<td>ABCC1 14008 G&gt;A</td>
<td>n/a</td>
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<tr>
<td>ABCC1 462 C&gt;T</td>
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<td>ABCC1 34215 C&gt;G</td>
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<td>ABCC2 156231 A&gt;G</td>
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<td>CES2 1647 C&gt;T</td>
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<td>n/a</td>
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<td>CYP3A5 22893 G&gt;A</td>
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<td>CYP3A5 30597 G&gt;A</td>
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<td>XRCC1 28132 G&gt;A</td>
<td>n/a</td>
</tr>
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</table>

* Number represents position in nucleotide sequence.
* Number represents amino acid codon.
* Number represents number of patients.
* Hardy-Weinberg notation was used for allele frequencies (p, q, and r).
* n/a = not available; CI, confidence intervals; Wt, Wild type patient; Het, Heterozygous variant type patient; Var, Homozygous variant type patient.

Table 5 | Summary of genotype-phenotype associations |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Polymorphism</td>
<td>Phenotypic consequence</td>
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<td></td>
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<tr>
<td>ABCB1 1236 C&gt;T</td>
<td>Irinotecan total AUC increased</td>
<td>0.038 (46)</td>
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<tr>
<td>SN-38 total AUC increased</td>
<td>0.031 (46)</td>
<td></td>
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<td>SN-38 lactone CL reduced</td>
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<tr>
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<td>Irinotecan lactone AUC</td>
<td>0.100 (59)</td>
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<tr>
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<td>Irinotecan lactone CL</td>
<td>0.083 (53)</td>
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<td>SN-38 lactone CL</td>
<td>0.127 (64)</td>
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<td>APC AUC</td>
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<td>UGT1A1*28</td>
<td>SN-38G/SN-38 AUC ratio</td>
<td>0.221 (53)</td>
<td></td>
</tr>
</tbody>
</table>

* Represents the best association (lowest $p$) between a given polymorphism (wild-type versus heterozygous variant versus homozygous variant type patients) and a change in a pharmacokinetic parameter, with number of patients in parenthesis.

* Kruskal-Wallis test following logarithmic transformation for data with a skewed distribution; except for ABCB1 1236 C>T, no statistically significant associations were found.

![Fig. 2 ABCB1 1236C>T variants in relation to the metabolic CL of SN-38 lactone. Wt, wild-type patient; Het, heterozygous variant type patient; Var, homozygous variant type patient.](Image 314x207 to 542x363)
Irinotecan Pharmacogenetics

The occurrence of multiple genetic defects. Furthermore, it has been
mentioned in literature for a normal Caucasian population (25). The
SN-38 glucuronidation rates and greater susceptibility to irino-
tecan-induced hematological and nonhematological toxicities
(30). Unfortunately, these results could not be confirmed in our
study, although the study settings were comparable. One reason
for this discrepancy may be found in the allele frequency of the
variant allele in our population that was clearly lower than
mentioned in literature for a normal Caucasian population (25).
However, although differences in our study among genotypes
were not statistically significant, an overall trend in reduced
SN-38 glucuronidation rate (i.e., REG) in homozygous variants
of UGT1A1*28 could be observed (Table 6), particularly in the
median values, both with pharmacokinetic data based on non-
compartmental analysis or those based on the NONMEM pop-
ulation model. Furthermore, it is particularly noteworthy that
one of the two patients with the variant UGT1A1 allele in our
study with data for REG was the only individual that experi-
enced grade 4 diarrhea in the entire cohort. Clearly, additional
investigation is required to unambiguously define the associa-
tion between genetic variation in UGT1A1 and irinotecan phar-
macokinetics and pharmacodynamics.

Novel SNPs in ABC1, ABC2, CES1, and CES2 were
identified and evaluated in this patient set. Because of the
rapid expansion of SNP discovery and the present lack of overlap
among the various SNP databases, it is possible that additional
functional polymorphisms in these genes are still to be described
(17). For example, recent data suggest that molecular determi-
nants of SN-38 glucuronidation and irinotecan response might
include common allelic variants of the hepatic UGT1A9
isozyme (31). This may eventually provide additional refine-
ment of the predictive strategies for irinotecan

One might seriously question if our current findings al-
ready provide meaningful tools for medical decision making in
clinical practice. It is probably too simplistic to think that the
complex metabolism of irinotecan can be predicted by screening
for one or even a few genetic variants. Because every individual
represents a combination of transporter and drug metabolizer
phenotypes and given the many enzymes involved in irinotecan
metabolism, it is apparent that some individuals are destined to
have unusual reactions to this agent because of the coincidental
occurrence of multiple genetic defects. Furthermore, it has been
shown before that various physiological and environmental fac-
tors are also involved in the way patients react to the irinotecan

UGT1A1*28 before treatment might identify patients with lower
SN-38 glucuronidation rates and greater susceptibility to irino-
tecan-induced hematological and nonhematological toxicities
(30). Unfortunately, these results could not be confirmed in our
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have unusual reactions to this agent because of the coincidental
occurrence of multiple genetic defects. Furthermore, it has been
shown before that various physiological and environmental fac-
tors are also involved in the way patients react to the irinotecan

therapy (2). Besides the condition of the patient and measures of
hepatic dysfunction, the role of comedication and dietary sup-
plements should not be underestimated. For example, sedatives,
antiepileptic drugs, and some corticosteroids, which are very
commonly used among patients on chemotherapy treatment, can
induce UGT1A1 and CYP3A4 activity (32, 33). In addition,
coadministration of a wide variety of agents can result in com-
petitive inhibition of CYP3A4 activity (34), whereas recom-
ended levels of the natural product St. John’s wort signifi-
cantly induce the activity of this enzyme, resulting in altered
SN-38 concentrations in plasma (35). Therefore, the next step in
predicting the pharmacokinetic and pharmacodynamic outcome
of therapy would be by focusing on phenotyping strategies
because these combine physiological, environmental, and genet-
ic factors. Hopefully, these procedures will eventually lead
toward individualized dosing of this drug. Trials implementing
a strategy to phenotype total CYP3A expression by using the
erthyromycin breath test and/or midazolam CL as surrogate
markers of enzyme activity before treatment with irinotecan are
currently ongoing.

In conclusion, individuals homozygous for the T allele of
ABCB1 1236 C>T appear to have altered irinotecan plasma
centration in comparison with heterozygous and wild-type
patients. Although this polymorphism does not completely ex-
plain the differences in irinotecan pharmacokinetics among pa-
ients, this observation may be of relevance to achieve individ-
ualized treatment strategies with this agent. Future studies will
focus on the inclusion of genotype data as a covariate in a
population model and will assess relationships between irinote-
can disposition and the rare variant genotypes, especially in
other ethnic groups.

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Table 6 Effect of UGT1A1*28 on the extent of SN-38 glucuronidation

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Reference</th>
<th>n</th>
<th>AUC&lt;sub&gt;0–t&lt;/sub&gt; (0–24 h) ratio&lt;sup&gt;a&lt;/sup&gt; SN-38G/SN-38</th>
<th>AUC&lt;sub&gt;0–inf&lt;/sub&gt; (0–100 h) ratio&lt;sup&gt;b&lt;/sup&gt; SN-38G/SN-38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt&lt;sup&gt;c&lt;/sup&gt;</td>
<td>This study</td>
<td>32</td>
<td>7.6 ± 4.1 (6.6)</td>
<td>6.9 ± 3.5 (6.4)</td>
</tr>
<tr>
<td></td>
<td>iy&lt;sub&gt;e&lt;/sub&gt; et al. (16)</td>
<td>9</td>
<td>9.3 ± 11</td>
<td>n/a</td>
</tr>
<tr>
<td>Het</td>
<td>This study</td>
<td>19</td>
<td>7.1 ± 3.6 (6.6)</td>
<td>6.7 ± 3.2 (6.1)</td>
</tr>
<tr>
<td></td>
<td>iy&lt;sub&gt;e&lt;/sub&gt; et al. (16)</td>
<td>7</td>
<td>4.0 ± 1.7</td>
<td>n/a</td>
</tr>
<tr>
<td>Var</td>
<td>This study</td>
<td>2</td>
<td>2.2, 5.2 (3.7)</td>
<td>2.5, 4.6 (3.6)</td>
</tr>
<tr>
<td></td>
<td>iy&lt;sub&gt;e&lt;/sub&gt; et al. (16)</td>
<td>4</td>
<td>2.4 ± 1.1</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<sup>a</sup> SN-38G/SN-38 AUC ratio based on nonparametric analysis of samples taken up to 24 h after irinotecan administration [trend analysis (Wt>Het>Var), P = 0.272].

<sup>b</sup> SN-38G/SN-38 AUC ratio based on NONMEM model [trend analysis (Wt>Het>Var), P = 0.300]; iy<sub>e</sub> et al. (16) [trend analysis (Wt>Het>Var), P = 0.001].

<sup>c</sup> Wt, Wild type patient; Het, Heterozygous variant type patient; Var, Homozygous variant type patient; n/a, not available.


Irinotecan Pathway Genotype Analysis to Predict Pharmacokinetics
